OUTCOMES AFTER MASSIVE HONEYBEE ENVENOMATION IN PATIENTS WITH COMORBID CONDITIONS DURING HOSPITAL ADMISSION: A RETROSPECTIVE REVIEW

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Abstract

This study's aim was to discover the outcomes associated with massive honeybee envenomation. Additionally, we wanted to observe what trends might be seen with regard to outcomes in patients with comorbidities and those without. Honeybees belong to the insect family of Hymenoptera, which includes wasps, yellow jackets and hornets. Hymenoptera are responsible for more deaths than any other venomous insects and pose a risk to the public due to the emergence of well-established populations of Africanized honeybees. These honeybees are prevalent in southwestern states such as Arizona. Africanized bees are more aggressive and take less to provoke stings than non-hybridized bees, and mass envenomations can cause fatal accidents. This study was a retrospective review of patient charts based on ICD-9 and ICD-10 records indicating massive honeybee envenomation and screened to include only patients meeting our inclusion criteria of ≥ 50 stings over a 10 year period at Banner – University Medical Center Phoenix. Patients were enrolled from charts between January 1, 2007 and October 20, 2016. 25 total patients were included and epidemiological, clinical, and therapeutic data were obtained compared for noticeable trends in the data with regard to demographic data and comorbidities. The 25 patients ranged in age from 16 to 82 years old. Total number of stings varied from an estimated 50 stings, to over 1000. The majority of patients were estimated to have been stung by between 100 to 500 bees representing thirteen patients (52%). Four patients (16%) had a history of CAD, fourteen patients had hypertension (56%), nine patients had diabetes (36%), and one patient had asthma. In terms of outcomes, five patients (20%) required intubation for airway management, two patients were dialyzed (8%), and the average length of stay was 84.2 hours over the course of hospital admission. Our results showed that there was no obvious trend in the outcomes of patients with and without CAD, asthma, hypertension, and diabetes. Notable trends were primarily seen in the total number of stings inflicted. In patients with a greater number of stings, the total length of stay increased dramatically. Number of stings also seemed to indicate a greater risk of requiring intubation as well. Finally, creatine kinase levels were also markedly elevated in patients with a higher sting count, supporting prior work done regarding the effect of mass envenomations with resulting rhabdomyolysis. This research supports that fact that ultimately the biggest

determinant of a patient's clinical course is the number of stings that they present with. It seems safe to assume that a mass envenomation on the scale of hundreds to thousands of stings will greatly increase the chance that this particular patient is going to have prominent rhabdomyolysis, be at greater risk of requiring advanced airway measures such as intubation, and be admitted to the hospital for a longer period. Future work would be enhanced by implementing a multicenter study to increase the power of the study to allow for statistical comparisons to be made to create an opportunity to delineate potential differences in outcomes based on comorbid conditions.

Table of Contents

List of Tables and Figures

Introduction

Honeybees belong to the insect family of Hymenoptera, which also includes wasps, yellow jackets and hornets. The stings from these insects can cause a range of clinical scenarios from mild symptoms to severe systemic reactions [4]. Massive honeybee envenomation by hundreds or even thousands of bees can lead to death due to the toxic effects of such a large quantity of venom [9]. Hymenoptera are responsible for more deaths than any other venomous insect [6, 11]. Massive honeybee envenomation poses a risk to the public due to the emergence of a well-established population of Africanized honeybees, especially in the southwestern states such as Arizona. Africanized bees are more aggressive and take less to provoke stings than non-hybridized bees, and mass envenomations can cause fatal accidents [10, 13]. The venom produced by the honeybees contains melittin, which is known for its lytic activity and cardiotoxicity on mammalian hearts [12]. Phospholipase A2 is another major component of bee venom and, along with melittin, can cause tissue damage including hemolysis and rhabdomyolysis [5, 8, 10]. Our retrospective clinical study aims to evaluate the outcomes following massive honeybee envenomation, paying particular attention to patients with pre-existing medical conditions and whether these are associated with a more severe emergency.

Coronary Artery Disease and Asthma comorbidities in massive envenomation

Studies have found that bee venom can have a direct toxic effect on the heart by inducing vasoconstriction, platelet aggregation and even thrombosis [7]. In one case, a 58-year-old woman reported chest tightness among other symptoms after being stung by 300 bees. Testing revealed ECG abnormalities along with a positive troponin I, and the patient was treated for angina until tests returned to normal. A study by Gueron et al. also discussed the effects of hymenoptera venom on cardiovascular health, mentioning ECG changes and rhythm abnormalities [6].

Another study highlighted the potential for myocardial ischemia following multiple bee stings, even in patients with normal coronary arteries. The causes of myocardial injury may be related to endothelial dysfunction, as well as the potential for thrombosis leading to myocardial ischemia, specifically in the coronary arteries [3, 13]. In our study we are interested in

determining the outcome of patients with a massive envenomation who had a prior diagnosis of coronary artery disease and how these patient outcomes might vary compared to those without an underlying cardiovascular pathology. Studies have also discussed various systemic reactions to honey bee envenomation including respiratory problems, which can occur in 0.3 – 7.5% of the population. These reactions can be life threatening and are typically IgE antibody mediated via reaction to honeybee venom [3]. Our study also aims to determine whether patients with a pre-existing respiratory condition such as asthma are more susceptible to a severe reaction following a massive envenomation.

Hemolysis

Various studies have included hemolysis as a symptom of envenomation by honeybees. Hemolysis is thought to be caused by components of honeybee venom including melittin and phospholipase A2, causing intravascular hemolysis due to cell membrane disruption [1]. The resulting hemolysis can be a contributing factor in renal failure and commonly occurs with other systemic effects including rhabdomyolysis [2, 4, 8], and could even be related to episodes of hemorrhage [3]. Hemolysis and the resulting hemoglobunuria and hemoglobinemia should be monitored in patients [9], and remains an important aspect to consider when treating the systemic effects of honeybee envenomation.

Rhabdomyolysis

Previous studies have shown that large quantities of venom can induce rhabdomyolysis due to the direct toxic effects of venom components, notably melittin and phospholipase A2 on cell membranes [13]. In one study an adolescent boy was stung 700 times while walking in the woods. He presented at the ER and was treated acutely and discharged within hours with normal vitals and the absence of other abnormalities. However, after 8 hours the patient returned to the ER in a worsened condition and was admitted, spending 6 days in the hospital. He had high creatinine and rhabdomyolysis as a result of the massive envenomation [5]. Another study highlighted that even a few stings can lead to rhabdomyolysis which was the case for a 34-year-old male who spent 5 days in a hospital with an elevated CPK due to honeybee venom induced rhabdomyolysis. Although a rare symptom of envenomation it is

important to recognize the potential for rhabdomyolysis especially in efforts to protect renal function by initiating early treatment [4].

Renal insufficiency

Previous research has shown that massive envenomation by honeybee stings have induced acute renal failure. In a study by Grisotto, et al., after injecting rats with Africanized honeybee venom, acute renal failure occurred via vasoconstriction of renal vessels, tubular toxicity and rhabdomyolysis. The main component of honeybee venom – melittin is likely the cause due to its effects on vascular endothelium, smooth muscle cells, arachidonic acid release, and the release of other vasoactive substances [1, 2].

Another report describes a 17-year-old Brazilian boy who was hospitalized after being stung by 1500 bees. Labs revealed high levels of creatinine and urea consistent with acute renal failure. Another child in this same report was stung 600 times and initially presented with high levels of creatinine and urea. In both cases the patient was admitted and remained in the hospital until kidney function returned to normal before being discharged [2]. These cases stress one of the more severe complications that can occur by massive honeybee envenomation and recognizing this event is crucial in the treatment and management of these events.

Length of stay

In a particular study regarding the treatment strategies for Africanized honeybee stings, patients who had suffered between 20 and 500 stings remained in the hospital for an average of three and a half days [13]. Length of stay will be an important factor to consider in our study while we examine the outcomes. Length of stay seems to vary depending on the individual presentation and the number of stings the patient presents with.

Number of stings

Research suggests that when the number of stings is less than 50, and the patient in question is not hypersensitive to bee venom, survival is very favorable with proper treatment [10]. Systemic toxicity is estimated to require a minimum of 50 stings in adults, and although rare, deaths via massive envenomation tend to occur between 500 and 1200 stings [5, 9, 10]. Betten

et al. has recommended that an adult with ≥50 stings and a child with more than one sting per kg of body weight constitutes observation for possible delayed toxicity effects, and monitoring of labs – particularly CPK levels [5]. Another report detailed recommendations for a 24-hour hospitalization period for pediatric patients and elderly patients with greater than 50 stings due to the potential for a delayed toxic reaction. A 6-hour observation was suggested for all other patients without symptoms other than pain [8].

Rationale

Various studies stress the importance of additional research required to fully elucidate the effects and treatment strategies for massive envenomations and the proper responses for emergency treatment [5, 8,] One study cited the "scant and variable" data available on the outcomes of massive envenomations [9]. Another study also described the importance of understanding the course of illness so that patients are not discharged prematurely only to return with a delayed onset toxic reaction [5]. There are also few reports on the cardiovascular effects after hymenoptera stings [6]. In reviewing the literature on massive honeybee envenomation it is clear that the information is limited. There does not seem to be a comprehensive review of a large set of patients who experienced massive envenomation, particularly patients in the United States. Most of the available literature is either composed of case reports or only study a handful of patients. By performing a retrospective review of the charts of patients who were admitted to Banner University Medical Center Phoenix for the diagnosis of massive honeybee envenomation, we could consolidate information regarding patient age, condition, health, and the outcomes of their envenomation. Using this information we can describe the treatment strategies provided and potentially highlight differences in individuals with pre-existing cardiovascular or respiratory conditions.

Our retrospective clinical study asks the following: what outcomes are associated with massive honeybee envenomation? Additionally, what trends might be seen with regard to outcomes in patients with comorbidities and those without. The comorbidities evaluated include: asthma, coronary artery disease, hypertension, and diabetes. Outcomes measured after massive envenomation include: acute kidney injury, rhabdomyolysis, hemolysis, need for

intubation or dialysis, and total length of hospital stay. It is our hope that further insights into the outcomes of mass envenomations may shed some light on major trends in the hospital course, and whether any trends are noticed in patients with comorbidities. The current literature on mass envenomations is often limited to various case reports, and the lack of larger scale studies is also a motive for our research. It is hoped that this will contribute to our understanding of the effects of a toxic venom load as well as have the potential to anticipate clinical sequelae, especially in vulnerable patient populations.

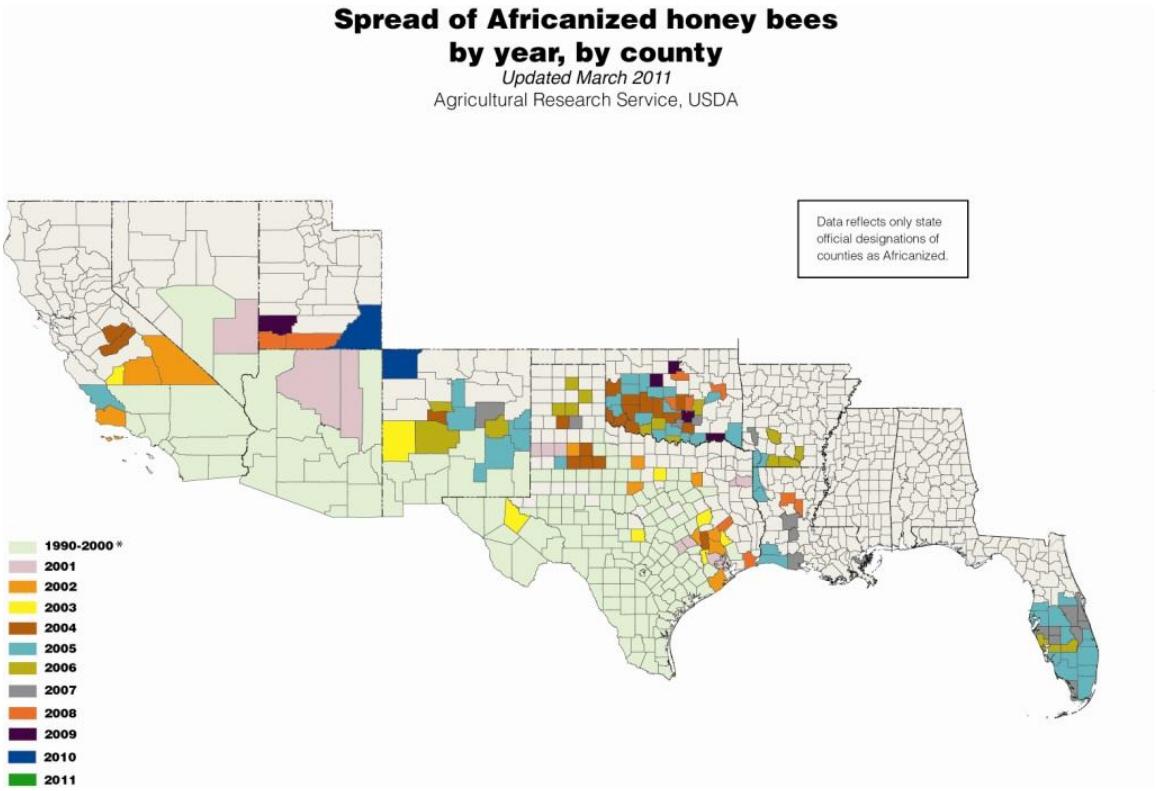

FIGURE 1. *Africanized honeybees have become well established in many southwestern states including Arizona, Nevada, New Mexico, Texas, southern California, Oklahoma, and even as far as Florida. (U.S. map of the spread of Africanized honey bees per year (1990 to 2011). From the Agricultural Research Service, (USDA 2011). Last modified: 06/26/2018.)*

Methods & Materials

This study was a retrospective analysis of patient charts based on ICD-9 and ICD-10 records indicating massive honeybee envenomation. Inclusion criteria were the following: all patients admitted to Banner – University Medical Center Phoenix between January 1, 2007 and October 20, 2016 with a diagnosis of massive honeybee envenomation. Exclusion criteria were: patients with less than 50 stings. Records were obtained through electronic medical records and any paper charts available for the selected time period. Over 500 charts were screened to exclude other forms of envenomation (scorpions, snakes, wasps, etc) as well as single bee stings resulting in anaphylaxis. A total of 25 patients met criteria and were included in the study. Each patient's chart was reviewed and de-identified information was collected in data abstraction sheets including epidemiological, clinical, and therapeutic data. The data was then transferred to a master list and each chart was assigned a unique identifier. Variables including age, weight, and past medical history were obtained for each patient. Outcomes were recorded based on patient's initial presentation, admission period, and discharge. Length of stay, and interventions such as intubation and need for dialysis were obtained through the chart review. Mean values were obtained for laboratory results during three periods of admission: presentation, peak/nadir, and discharge. Descriptive statistics were used to display the data collected for demographics and outcomes. The study sponsor was Banner – University Medical Center Phoenix, Medical Education, and Medical Toxicology Fellowship. The study received approval from the Banner Health IRB – Phoenix Panel.

Results

The 25 patients ranged in age from 16 to 82 years old, averaging 60.5 years, with a mean weight of 79.9kg. Fifteen (60%) were male, ten were female. Total number of stings varied from an estimated 50 stings, to over 1000. The majority of patients were estimated to have been stung by between 100 to 500 bees representing thirteen patients (52%). Four patients (16%) had a history of coronary artery disease, fourteen patients had hypertension (56%), nine patients had diabetes (36%), and one patient (4%) had asthma. In terms of outcomes five patients (20%) required intubation for airway management, two patients were dialyzed (8%), and the average length of stay was 84.2 hours over the course of hospital admission. Laboratory values for creatine kinase at their peak show 11 patients (44%) with levels over 1000 U/L. Peak creatinine was greater than 2.0mg/dL in six (24%) patients, while hemoglobin only dropped below 8.0g/dL in two (8%) patients. Table 1 summarizes these data, including values for Hgb, CK, and Creatinine values at presentation to the hospital as well as discharge values. Since this study was too small to statistically compare the outcomes with the continuous variables obtained, descriptive statistics were used to present the results. Table 2 and 3 show the results obtained for outcomes in relation to patient demographics and comorbid conditions.

Table 1. Demographics & Outcomes	
Variables	Values N=25
Age, years (mean, SD)	60.5 (15.3)
Gender (male, %)	15 (60.0)
Weight, kg (mean, SD)	79.9 (18.4)
Stings (n, %)	
50	2 (8.00)
51 – 100	8 (32.0)
101 – 500	13 (52.0)
501 - 1000+	2 (8.00)
CAD (yes, %)	4 (16.0)
Asthma (yes, %)	1 (4.00)
Hypertension (yes, %)	14 (56.0)
Diabetes Mellitus (yes, %)	9 (36.0)
Outcomes (yes, %)	
Hgb < 8.0 Presentation	1 (4.00)
Hgb < 8.0 Nadir	2 (8.00)
Hgb < 8.0 Discharge	0 (0.0)
CK > 1000 Presentation	3 (12.0)
CK > 1000 Peak	11 (44.0)
CK > 1000 Discharge	8 (32.0)
Creatinine > 2.0 Presentation	4 (16.0)
Creatinine > 2.0 Peak	6 (24.0)
Creatinine > 2.0 Discharge	4 (16.0)
Intubated (yes, %)	5 (20.0)
Dialysis (yes, %)	2 (8.00)
Total LOS, hours (mean, SD)	84.2 (118.7)

Table 1: Patient Demographics variables and outcomes among all patients with mass envenomations.

Table 2 Demographics/Comorbidities and values for Hemoglobin, Creatine Kinase, and Creatinine									
	Hemoglobin			CK Level			Creatinine		
Variables	Pres.	Nadir	Discharge	Pres.	Peak	Discharge	Pres.	Peak	Discharge
	Mean (g/dL)			Mean (U/L)			Mean (mg/dL)		
Gender									
Female	12.8	11.3	11.5	247	1644	2551	1.36	1.36	1.11
Male	14.9	11.8	12.5	4068	10236	2199	2.29	2.65	1.97
Stings									
50	14.2	11.4	11.4	116	125	125	1.33	1.35	1.15
51 – 100	15.1	13.9	13.5	511	572	397	1.08	1.19	0.95
101 – 500	13.9	11.8	11.8	3425	990	3333	2.39	2.56	1.89
501 - 1000	10.6	8.85	9	301	24102	3250	0.8	3.95	3.08
CAD									
No	14.2	11.6	12.1	2987	8972	2621	1.77	2.11	1.59
Yes	13.3	11.5	12.5	555	3330	1110	2.3	2.3	1.83
Asthma									
No	13.9	11.5	12	2686	8555	2416	1.85	2.13	1.63
Yes	17.6	14.5	14.5	814	814	682	2.1	2.1	1.44
Hypertension									
No	13.5	10.1	11.3	5695	12564	1762	2.45	2.98	1.67
Yes	14.4	12.6	12.8	601	5184	2685	1.46	1.47	1.59
Diabetes									
No	13.9	10.9	11.7	3614	11794	2554	2.07	2.44	1.43
Yes	14.3	12.6	12.9	519	3016	1974	1.5	1.59	1.67

Table 2. shows the comparison of the continuous variables with the laboratory values for hemoglobin, creatine kinase, and creatinine during hospital admission. Presentation, peak/nadir, and discharge values for each lab are displayed using the mean.

Table 3. Demographics/Comorbidities with relation to Intubation or Dialysis, and Length of Stay			
Variables	Intubation	Dialysis	Total Length of Stay
	N, %	N, %	Mean (hrs)
Gender			
Female	1 (10.0)	0 (0.0)	44.3
Male	4 (26.7)	2 (13.3)	110.7
Stings			
50	0 (0.0)	0 (0.0)	22.3
51 – 100	1 (12.5)	0 (0.0)	28.6
101 – 500	2 (15.4)	1 (7.69)	104
501 - 1000	2 (100.0)	1 (50.0)	236.5
CAD			
No	5 (23.8)	2 (9.52)	85.2
Yes	0 (0.0)	0 (0.0)	78.6
Asthma			
No	5 (20.8)	2 (8.33)	87.1
Yes	0 (0.0)	0 (0.0)	12.5
Hypertension			
No	3 (27.3)	2 (18.2)	121.2
Yes	2 (14.3)	0 (0.0)	55
Diabetes			
No	4 (25.0)	2 (12.5)	99.6
Yes	1 (11.1)	0 (0.0)	56.6

Table 3. shows the comparison of the continuous variables and the instances of intubation, dialysis, and length of stay.

Discussion

The primary question asked was what outcomes are associated with massive honeybee envenomation and can we see trends in outcomes between patients with comorbid conditions and those without? Our results show that there were no obvious trends with respect to the outcomes seen in patients with and without CAD, asthma, hypertension, and diabetes. Because of the small sample size, any real differences in outcomes would be impossible to detect statistically, and ultimately we were limited by an underpowered study. There were, however, some trends noticed in outcomes with relation to demographic data, primarily seen in the total number of stings inflicted. In patients with a greater number of stings, the total length of stay increased dramatically. Patients who had 50 to 100 stings had an average length of stay of about 28 hours, but in patients in the range of hundreds of stings the average stay went up to 104 hours, and with stings over 500, the average length of stay was 236 hours. This highlights the importance of the impact of the total toxic venom load in mass envenomations of this caliber. While again being unable to report any statistical differences using our data, there was also a clear trend towards requiring intubation as an intervention as the number of stings became greater.

With regard to laboratory outcomes, peak creatine kinase measurements were markedly higher in patients with a greater number of stings. This finding supports other literature confirming rhabdomyolysis as a common outcome of massive envenomation. A component of bee venom – melittin – is thought to cause rhabdomyolysis via the mechanisms by which it inserts itself into the phospholipid bilayer of cell membranes, ultimately causing cell disruption. Phospholipase A2 further damages cell membranes and may also play a role in rhabdomyolysis. Again, total number of stings seems to be the primary difference in the severity of rhabdomyolysis, as evidenced in Table 2 – the patients on discharge who had more stings (>100), still have a greater CK level than patients with fewer total stings. Peak creatinine was also found to be higher in male patients. The reason for this difference could be an issue regarding total body mass, in which patients with more muscle mass may be slightly more affected by the resulting rhabdomyolysis and myoglobinemia after a mass envenomation. This

would in turn affect the function of the kidneys resulting in an acute kidney injury while raising creatinine levels. Age did not appear to play a significant factor in any of the outcome variables measured, with no obvious trends observed.

This project supports that fact that ultimately the biggest determinant of a patient's clinical course is the number of stings that they present with. It seems safe to assume that a mass envenomation on the scale of hundreds to thousands of stings will greatly increase the chance of significant rhabdomyolysis, risk of requiring intubation, and greatly increased hospital stay. This research project is not without its weaknesses, of which the primary concern is the total number of patients included in this study. Even having gone back through 10 years worth of patient charts at a major institution in a southwestern state affected by Africanized honeybees, only 25 patient charts met our inclusion criteria. This highlights the rarity of this type of clinical scenario, but also supports why research in this area is important for when these events do occur. Because this study was limited by a small sample size, the power of this research would be greatly enhanced by the inclusion of many more patient samples to help delineate if any comorbid conditions may in fact play a significant role in outcomes.

Future Directions

Future research could use a multi-institutional approach to capture a larger pool of patients needed to perform a more robust statistical analysis on outcomes and whether in fact comorbid conditions could play a significant role in outcomes. New research could also separate pediatric patients to further delineate the work to include age as a predisposing factor to determine whether comorbid conditions plays a role in these distinct populations.

Conclusions

In summary, our research has supported prior work on massive envenomation with regard to envenomation severity. In patients high a higher sting count, the outcomes had a clear trend towards worsened laboratory values as well as greater risk of interventions. We found that ultimately the largest determinant of a patient's clinical course was the number of stings inflicted during the bee attack. When patients are stung by hundreds and even thousands of bees, the likelihood of resulting rhabdomyolysis, advanced airway measures, and lengthened hospital stay increased based on our findings. This study helps add to a limited fund of knowledge regarding mass envenomation scenarios, and sheds light on the clinical course of patients, especially those in severe envenomation. While being limited by an underpowered study, this information adds to a field of research that is lacking larger robust studies, and may help solidify the importance of how sting number may impact a patient's clinical course.

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